**ACR Open Rheumatology**
Vol. 2, No. 4, April 2020, pp 197–206
DOI 10.1002/acr2.11126
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# Increased Mortality in Asians With Systemic Sclerosis in Northern California

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**Objective.** The objective of this study is to evaluate racial/ethnic differences in disease manifestations and survival in a US cohort of patients with systemic sclerosis (SSc), with a focus on Asian patients.

**Methods.** A retrospective cohort study was conducted among Kaiser Permanente Northern California adults with an incident SSc diagnosis by a rheumatologist from 2007 to 2016, confirmed by a chart review to fulfill 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. Self-reported race/ethnicity was categorized as non-Hispanic white, Asian, Hispanic, and black. Disease manifestations and survival were compared, using white patients as the reference.

**Results.** A total of 609 patients with incident SSc were identified: 89% were women, and 81% had limited cutaneous SSc, with a mean age at diagnosis of 55.4 ± 14.8 years. The racial/ethnic distribution was 51% non-Hispanic white (n = 310), 25% Hispanic (n = 154), 16% Asian (n = 96), and 8% black (n = 49). Compared with white patients, black patients had a greater prevalence of diffuse disease (14.5% vs. 44.9%; $P < 0.001$), and Asians had higher rates of anti-U1-RNP antibodies (32.1% vs. 11.9%; $P = 0.005$). Nine-year overall survival rates following SSc diagnosis were lower in Asian (52.3%), black (52.2%), and Hispanic patients (68.2%) compared with white patients (75.8%). Pulmonary hypertension and infections were the leading causes of death in Asian patients. Asian race was associated with higher mortality on univariable (hazard ratio [HR] 1.83 [95% confidence interval (CI) 1.08-2.99]; $P = 0.020$) and multivariable analyses (HR 1.80 [95% CI 0.99-3.16]; $P = 0.047$) when adjusting for age, sex, body mass index, cutaneous subtype, smoking status, interstitial lung disease, pulmonary hypertension, renal crisis, and malabsorption syndrome.

**Conclusion.** Asian patients with SSc in this US cohort had increased mortality compared with white patients. These patients warrant close monitoring for disease progression.

## INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by excessive collagen deposition, vascular damage, inflammation, and progressive fibrosis of the skin and visceral organs (1). Race has a significant influence on the epidemiology, clinical manifestations, survival, autoantibody frequencies, and genetic factors in SSc (2).

Multiple studies in black and white patients have implicated the interaction between racial background, autoantibody subtype, and genetic factors in determining disease manifestations, severity, and progression in SSc (3,4). Black patients have been reported to have a more severe clinical phenotype (5), with a younger age at SSc onset (6,7), a higher frequency of diffuse skin involvement (6), more extensive pulmonary disease (7,8), a higher risk for scleroderma renal crisis (9), and an overall worse prognosis (including higher mortality), compared with white patients (10–12).

Studies examining clinical characteristics and outcomes in Asian patients with SSc living in Asian countries suggest a more severe clinical phenotype in this racial group as well. Chinese

Funding support was provided by Kaiser Permanente Northern California Graduate Medical Education Research. Dr. M. P. Chung's work was supported by the Training Program in Adult and Pediatric Rheumatology (5T32AR050942-12). Dr. L. Chung's work was supported by the Scleroderma Research Foundation.

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Ms. Postlethwaite is an investigator on an unrelated US Food and Drug Administration–mandated safety study funded by Bayer Global and administered through the Kaiser Foundation Research Institute. No other disclosures relevant to this article were reported.

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Submitted for publication December 19, 2019; accepted in revised form February 18, 2020.

**SIGNIFICANCE & INNOVATIONS**

- This is the first study to compare racial/ethnic differences in patients with systemic sclerosis (SSc) using the Kaiser Permanente Northern California population, with a focus on Asian patients.
- Compared with white patients, Asian patients were found to have increased mortality and higher rates of anti-U1-RNP antibodies.
- Pulmonary hypertension and infections were the leading causes of death in Asian patients. Further research is needed to externally validate these findings and to identify both genetic and environmental determinants of SSc disease expression in different racial groups.

patients with SSc had unique serological and clinical features, with higher frequencies of anti-Scl-70 antibodies, diffuse cutaneous disease, and pulmonary fibrosis but lower anti-RNA polymerase III antibody frequency compared with US white patients from a prospective registry (13). In the Singapore SSc Cohort, Chinese patients with SSc had higher rates of the diffuse cutaneous subtype, an earlier age at diagnosis, more severe pulmonary arterial hypertension, and a different autoantibody profile (characterized by higher frequencies of anti-Scl-70, anti-U1-RNP, and anti-SSA/Ro but lower anticentromere antibodies) compared with historical cohorts of US white patients (14). Thai patients have been shown to have higher frequencies of diffuse skin disease and positive anti-Scl-70 antibodies compared with white Australians from the same clinic (15). However, most of these studies were limited by the use of indirect racial comparisons, their cross-sectional design, and lack of outcome assessment. One small study of North American white (n = 47), black (n = 15), and Japanese (n = 43) patients with SSc and anti-Scl-70 antibodies found that Japanese and black patients were more likely to develop severe lung disease and had higher mortality rates compared with white patients (3).

To date, limited research has been published on Asian patients with SSc living in the United States compared with patients of other racial/ethnic groups. In 2009, Schmajuk et al (16) performed a pilot cross-sectional study to compare disease features by race in patients evaluated at Stanford University and affiliated hospitals. Asian Americans were less likely to have digital ulcers or anemia than white patients, but there were no other significant differences in disease manifestations. This study lacked follow-up to evaluate survival and long-term disease outcomes, and similar to the studies discussed previously, it was underpowered to capture important clinical differences between racial groups.

The purpose of this study was to evaluate racial/ethnic disparities in clinical characteristics, autoantibody profiles, and survival in patients with SSc. We used data from Kaiser Permanente Northern California (KPNC), a large integrated health care system with a well-defined diverse patient population representative of the Northern California geographic region (17). This study setting offered a robust Asian American population, follow-up on outcomes, and direct comparisons across racial/ethnic groups. Such comparisons may provide insight into the relative importance of race and genetic background versus environmental factors in the onset and expression of SSc. Our findings may also guide appropriate treatment, monitoring, and prognostication among different groups in the context of an increasing racial diversity in the US population.

## MATERIALS AND METHODS

**Setting.** KPNC is a large demographically diverse integrated health care delivery system caring for more than 4.2 million members in Northern California (including Medicare beneficiaries), composing one-third of the insured population in the area (17). This insured population is socially, economically, and racially/ethnically diverse (17). Members within KPNC receive comprehensive health care services, including preventive, ambulatory, emergency, and inpatient care, as well as laboratory, radiology, and pharmacy services. Members are cared for by physicians from the Permanente Medical Group, a self-governed, physician-led, prepaid, multispecialty medical group. This study was approved by the Kaiser Foundation Research Institute and Stanford University Institutional Review Boards, with waiver of signed consent.

**Study design and population.** We performed a retrospective cohort study using electronic medical records for all eligible KPNC adults with an incident diagnosis of SSc by a rheumatologist between January 1, 2007, and December 31, 2016. The start date was chosen after the regional implementation of electronic medical records at KPNC in 2006. Participants were first identified using the *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) diagnosis codes for SSc (ICD-9: 710.1; ICD-10: M34) during the study period and were required to have at least one clinic visit with a rheumatologist. A subsequent medical record review was performed to ensure that only patients who fulfilled 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for definite SSc (18) were included in this study. Self-reported race/ethnicity was categorized as: non-Hispanic white, Asian (including Pacific Islander), black, and Hispanic white (excluding Asian and black) (19). Multiracial and other racial subgroups were excluded from this study because we did not have ancestry data. Incident cases were defined as patients with a new diagnosis of SSc at KPNC from 2007 onward (confirmed by a medical record review), and patients were required to have KPNC membership for a minimum of 12 months prior to SSc diagnosis. Prevalent cases (defined as having an SSc diagnosis prior to 2007 or carrying a diagnosis from an outside rheumatologist prior to KPNC membership) were excluded to avoid immortal time bias.

**Clinical variables and autoantibodies.** Data were obtained by electronic database extraction from KPNC's clinical electronic health record. Demographic information was collected, including sex, race/ethnicity, smoking status, and body mass index (BMI) at diagnosis. Disease subtype based on the extent of skin involvement (limited vs. diffuse cutaneous SSc), age at diagnosis, and age at symptom onset were collected. Date of diagnosis was defined as the date of first SSc diagnosis definitively made by a KPNC rheumatologist, according to an electronic medical record review of physician documentation.

Clinical manifestations of SSc were collected by organ system through electronic medical record review. Given that disease features may vary with time, we characterized the involvement of each organ system by its most severe expression at any recorded visit:

1. Vascular involvement included telangiectasias, Raynaud's phenomenon, digital gangrene, digital ulcers, and calcinosis.
2. Musculoskeletal involvement included joint pain, joint contractures, and myositis.
3. Cardiac involvement included congestive heart failure (defined as diastolic heart failure or systolic heart failure with impaired left ventricular function with an ejection fraction less than 50% on echocardiogram).
4. Pulmonary disease included interstitial lung disease (diagnosed by a pulmonologist or radiologist with high-resolution computed tomography [CT] of the chest), chronic oxygen dependence, or history of lung transplantation. Suspected pulmonary hypertension was denoted for all patients with an estimated right ventricular systolic pressure greater than or equal to 40 mm Hg on Doppler echocardiography, as previously reported (20). For the subset of patients whose physician pursued a right heart catheterization (RHC) evaluation, pulmonary arterial hypertension was defined by a resting mean pulmonary artery pressure greater than or equal to 25 mm Hg in the setting of a pulmonary capillary wedge pressure less than or equal to 15 mm Hg.
5. Gastrointestinal involvement was noted for symptomatic gastroesophageal reflux, malabsorption syndrome, or small intestinal bacterial overgrowth.
6. Renal involvement included scleroderma renal crisis, kidney transplant, or dialysis dependence.

We documented the following serologic autoantibody results for each study subject: antinuclear antibody (ANA) with immunofluorescent staining pattern (positive value defined as ≥1:80), anticentromere, anti-Scl-70 (topoisomerase I), anti-SSA/Ro, anti-SSB/La, and anti-U1-RNP (ribonucleoprotein). RNA polymerase III was excluded from analysis because of excessive missing data. Although serologic antibodies may vary with time, we considered an individual seropositive if antibodies exceeded standard laboratory ranges at any point in time. Data for the ANA pattern were collected when available, namely if indirect immunofluorescence was ordered at the discretion of the individual rheumatologist.

Ever usage of immunosuppressant medications for each patient with SSc was abstracted from physician notes and pharmacy data and included mycophenolate mofetil, methotrexate, cyclophosphamide, azathioprine, low-dose and high-dose prednisone (defined as less than or equal to 20 mg and greater than 20 mg, respectively), intravenous immunoglobulin (IVIG), and rituximab. Prescribing practices for immunosuppressant medications were up to the discretion of the treating rheumatologist and/or pulmonologist.

**Outcomes.** The primary outcome of interest was overall survival rates by racial/ethnic group, measured from the date of SSc diagnosis. Primary causes of death for all deceased patients were ascertained through an electronic chart review of hospital discharge summaries or physician death notes and categorized as previously defined (21).

**Statistical analysis.** Descriptive statistics (frequencies, proportions, means, and medians) were used to describe the demographic and clinical characteristics of the four racial/ethnic groups. $\chi^2$ tests or Fisher's exact tests were used to compare categorical variables, as appropriate. Analysis of variance was used to compare the means for continuous variables across the four racial/ethnic groups. When the overall comparisons among the four racial/ethnic groups were statistically significant, we performed multiple comparisons using the Fisher method of adjusting the *P* value to assess paired comparisons for significance (implemented using the PROC MULTTEST procedure in SAS [SAS Institute, Inc.]).

The Kaplan-Meier method was used to compare 5-year and 9-year survival rates between white, Asian, black, and Hispanic patients. Participants were censored at the earliest of the following: lost to follow-up (defined as end of KPNC membership), death, or end of study period (December 31, 2016). Differences in survival were assessed by the log-rank test. Univariable and multivariable Cox regression analyses were performed to determine which demographic and clinical variables were predictive of death. The proportionality of hazards assumption was met. Predictors used in the model included those that were statistically significant in the univariable analysis as well as those generally accepted in the literature to be potential predictors of mortality. Cases that were missing variables in the multivariable model were dropped from analysis, leaving only cases with complete data available. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc.), with the threshold of significance set at *P* is less than 0.05.

## RESULTS

**Study population characteristics.** A total of 609 KPNC adult incident patients with SSc were identified (Table 1). Most were female (89%) and had limited cutaneous SSc (81%). Mean age at diagnosis was 55.4 ± 14.8 years and mean disease

**Table 1.** Baseline demographics of SSc cohort by race/ethnicity

| Characteristics (n = Patients With Complete Data) | Overall (N = 609) | Asian (n = 96; 16%) | Black (n = 49; 8%) | Hispanic (n = 154; 25%) | White (n = 310; 51%) | $P^a$ |
|---|---|---|---|---|---|---|
| Female sex (n = 609), n (%) | 544/609 (89.3) | 85/96 (88.5) | 39/49 (79.6) | 141/154 (91.6) | 279/310 (90.0) | 0.117 |
| Diffuse (n = 609), n (%) | 116/609 (19.0) | 21/96 (21.9) | **22/49 (44.9)**** | 28/154 (18.2) | 45/310 (14.5) | **<0.001** |
| BMI (kg/ma) (n = 560), mean ± SD | 26.6 ± 5.9 | **23.9 ± 4.9**** | 28.5 ± 6.2 | 27.7 ± 5.2 | 26.6 ± 5.3 | **<0.01** |
| Ever smoker (n = 568), n (%) | 187/568 (32.9) | **16/92 (17.4)**** | 20/48 (41.7) | **29/146 (19.9)**** | 122/282 (43.3) | **<0.001** |
| Age at diagnosis of SSc by rheumatologist (n = 609), y, mean ± SD | 55.4 ± 14.8 | **51.7 ± 16.3**** | **53.1 ± 12.9*** | **52.8 ± 14.5**** | 58.9 ± 14.1 | **<0.001** |
| Time from first non-Raynaud symptom to SSc diagnosis (n = 529), y, mean ± SD | 4.9 ± 3.8 | 4.2 ± 3.5 | 3.9 ± 1.8 | 4.2 ± 2.8 | 5.5 ± 4.5 | 0.168 |
| Positive ANA (n = 578), n (%)[b] | 508/572 (88.9) | 81/93 (87.1) | 40/44 (90.9) | 143/152 (94.1) | 244/283 (86.2) | 0.131 |
| Nuclear ANA (n = 379), n (%) | 54/379 (14.2) | 8/57 (14.0) | 10/36 (27.8) | 10/99 (10.1) | 26/187 (13.9) | 0.078 |
| Anticentromere (n = 543), n (%) | 291/543 (53.6) | 42/92 (45.7) | 12/42 (28.6) | 92/143 (64.3) | 145/266 (54.5) | **<0.001** |
| Anti-SCL-70 (n = 510), n (%) | 98/510 (19.2) | 23/90 (25.6) | 10/45 (22.2) | 27/138 (19.6) | 38/237 (16.0) | 0.246 |
| Anti-SSA/Ro (n = 467), n (%) | 69/467 (14.8) | 18/81 (22.2) | 5/36 (13.9) | 19/126 (15.1) | 27/224 (12.1) | 0.178 |
| Anti-SSB/La (n = 463), n (%) | 19/463 (4.1) | 7/79 (8.9) | 1/37 (2.7) | 4/126 (3.2) | 7/221 (3.2) | 0.139 |
| Anti-U1RNP (n = 460), n (%) | 77/460 (16.7) | **26/81 (32.1)**** | 4/38 (10.5) | 21/123 (17.1) | 26/218 (11.9) | **<0.001** |
| SLE overlap, n (%) | 21/77 (27.3) | 6/26 (23.1) | 2/4 (50.0) | 10/21 (47.6) | 3/26 (11.5) | **0.031** |

Abbreviation: ANA, antinuclear antibody; BMI, body mass index; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
[a]$\chi^2$ test or Fisher's exact test for categorical variables; one-way analysis of variance for continuous variables.
[b]Positive ANA by immunofluorescence (≥1:80) (n = 379) or BioPlex 2200 ANA screen (n = 199). For nuclear ANA, denominators represent patients with available data.
*$P$ < 0.05 when comparing with white patients; **$P$ < 0.01 when comparing with white patients.
Statistically significant values (defined as $P$ < 0.05) are in bold.

duration from first non-Raynaud symptom to SSc diagnosis was 5 ± 5 years. The racial/ethnic distribution was composed of 51% white (n = 310), 25% Hispanic (n = 154), 16% Asian (n = 96), and 8% black (n = 49) patients. Self-reported ancestry of Asian patients included the following in descending frequency: Filipino (n = 24; 25.0%), Chinese (n = 23; 24.0%), Indian (n = 13; 13.5%), Japanese (n = 5; 5.2%), Vietnamese (n = 5; 5.2%), Korean (n = 4; 4.2%), Pacific Islander (n = 3; 3.1%), and not specified (n = 19; 19.8%).

The mean age at SSc diagnosis for white patients (58.9 ± 14.1 years) was significantly older compared with all other groups. There were no significant differences in disease duration by race/ethnicity. In pairwise comparisons, black patients had a higher prevalence of diffuse cutaneous SSc (44.9% vs. 14.5%; $P$ < 0.001) compared with white patients. Asian (17.4% vs. 43.3%; $P$ < 0.001) and Hispanic patients (19.9% vs. 43.3%; $P$ < 0.001) were significantly less likely to have ever smoked compared with white patients. Asian patients had the lowest mean BMI of all groups.

The majority of the cohort had at least one echocardiogram to evaluate for pulmonary hypertension (n = 508; 83.4%) and/or at least one high-resolution chest CT scan to evaluate for interstitial lung disease (n = 570; 93.6%). Of patients with suspected pulmonary hypertension on echocardiogram (n = 154), approximately one-third (n = 50) underwent RHC to evaluate for pulmonary arterial hypertension. Thirty patients had a confirmed diagnosis of pulmonary arterial hypertension on RHC (4.9% of the entire cohort). Decision to proceed with RHC was up to the discretion of the physician team and patient. Common reasons for declining RHC included borderline echocardiogram results, invasive interventions declined by patient, medical comorbidities, and/or potential risks of the procedure.

**Autoantibodies.** Asian patients had a significantly higher prevalence of anti-U1-RNP antibodies compared with white patients (32.1% vs. 11.9%; $P$ = 0.005). Across all racial/ethnic groups, Asian patients had the highest prevalence of anti-Scl-70 (25.6%) and anti-SSA/Ro antibodies (22.2%), whereas black patients had the lowest prevalence of anticentromere antibodies (28.6%), but these results were not statistically significant when adjusting for pairwise comparisons.

**Organ involvement.** Clinical manifestations in Asian, black, and Hispanic patients were not significantly different from those in white patients after adjusting for multiple pairwise comparisons (Table 2).

**Survival analyses.** Cumulative death for the entire cohort was 17.2% (105 deaths/609 patients) over a median follow-up time of 5 years. Cumulative death by race for white, Hispanic, Asian, and black patients was 48/310 (15.5%), 23/154 (14.9%), 22/96 (22.9%), and 12/49 (24.5%), respectively. The total proportion of patients censored because of KPNC membership ending prior to study end was 14.5%, whereas 68.3% of patients were alive at study end. There were no statistically significant differences in types of censorship by race/ethnicity (Supplementary Table 1). The median (interquartile range) follow-up time for

**Table 2.** Organ involvement of systemic sclerosis cohort by race/ethnicity

| Characteristics (n = Patients With Complete Data) | All (N = 609), n (%) | Asian (n = 96), n (%) | Black (n = 49), n (%) | Hispanic (n = 154), n (%) | White (n = 310), n (%) | P[a] |
|---|---|---|---|---|---|---|
| Vascular | | | | | | |
| Telangiectasias (n = 496) | 376/496 (75.8) | 48/71 (67.6) | 20/36 (55.6)[c] | 97/129 (75.2) | 211/260 (81.2) | 0.002 |
| Raynaud phenomenon (n = 603) | 583/603 (96.7) | 93/96 (96.9) | 42/48 (87.5)[c] | 144/150 (96.0) | 304/309 (98.4) | 0.004 |
| Digital gangrene (n = 609) | 48/609 (7.9) | 4/96 (4.2) | 6/49 (12.8) | 15/154 (9.8) | 23/310 (7.4) | 0.239 |
| Digital ulcers (n = 437) | 205/437 (46.9) | 33/62 (53.2) | 22/35 (62.9) | 59/106 (55.7) | 91/234 (38.9) | **0.003** |
| Calcinosis (n = 608) | 140/608 (23.0) | 11/96 (11.5) | 9/48 (18.8) | 39/154 (25.3) | 81/310 (26.1) | **0.020** |
| Musculoskeletal | | | | | | |
| Joint pain (n = 593) | 460/593 (77.6) | 71/94 (75.5) | 42/49 (85.7) | 122/152 (80.3) | 225/298 (75.5) | 0.326 |
| Joint contractures (n = 608) | 154/608 (25.3) | 22/96 (22.9) | 13/49 (26.5) | 39/153 (25.5) | 80/310 (25.8) | 0.946 |
| Myositis (n = 608) | 48/608 (7.9) | 6/96 (6.3) | 5/48 (10.4) | 11/154 (7.1) | 26/310 (8.4) | 0.801 |
| Cardiopulmonary | | | | | | |
| Congestive heart failure (n=515) | 97/515 (18.8) | 12/84 (14.3) | 8/37 (21.6) | 20/133 (15.0) | 57/261 (21.8) | 0.249 |
| Suspected pulmonary hypertension on echocardiogram (n = 508) | 154/508 (25.3) | 26/81 (32.1) | 16/40 (40.0) | 34/125 (27.2) | 78/262 (29.7) | 0.474 |
| Pulmonary arterial hypertension (n = 50)[b] | 30/50 (60.0) | 4/8 (50.0) | 3/5 (60.0) | 7/10 (70.0) | 16/26 (61.5) | 0.867 |
| Interstitial lung disease (n = 570) | 219/570 (38.4) | 36/85 (42.4) | 26/46 (56.5) | 56/144 (38.9) | 101/295 (34.2) | **0.028** |
| Oxygen dependence (n = 608) | 83/608 (13.7) | 13/96 (13.5) | 10/49 (20.4) | 22/154 (14.3) | 38/309 (12.3) | 0.488 |
| Gastrointestinal | | | | | | |
| Gastroesophageal reflux (n = 574) | 500/574 (87.1) | 74/85 (87.1) | 41/44 (93.2) | 133/148 (89.9) | 252/297 (84.9) | 0.284 |
| Malabsorption syndrome or small intestinal bacterial overgrowth (n = 603) | 44/603 (7.3) | 7/94 (7.5) | 3/49 (6.1) | 16/152 (10.5) | 18/308 (5.8) | 0.333 |
| Renal | | | | | | |
| Renal crisis (n = 609) | 19/609 (3.1) | 5/96 (5.2) | 1/49 (2.0) | 5/153 (3.3) | 8/310 (2.6) | 0.598 |
| Dialysis dependence (n = 603) | 14/603 (2.3) | 1/95 (1.1) | 4/48 (8.3) | 5/153 (3.3) | 4/307 (1.3) | **0.016** |

[a] $\chi^2$ test or Fisher's exact test for categorical variables.
[b] Subset of patients who pursued right heart catheterization.
[c] $P < 0.10$ when comparing with white patients.
Statistically significant values (defined as $P < 0.05$) are in bold.

white, Hispanic, Asian, and black patients was 5.1 (2.3-8.4), 4.5 (1.8-8.1), 4.7 (2.0-7.9), and 5.4 (2.4-9.9) years, respectively.

Kaplan-Meier survival analyses showed that Asian and black patients had increased overall mortality compared with white and Hispanic patients (Figure 1). Five-year overall survival rates from the date of SSc diagnosis for white, Hispanic, Asian, and black patients were 85.3%, 86.4%, 76.4%, and 76.2%, respectively. Nine-year overall survival rates from the date of diagnosis for white, Hispanic, Asian, and black patients were 75.8%, 68.2%, 52.3%, 52.2%, respectively ($P = 0.057$).

Asian (hazard ratio [HR] 1.83 [95% confidence interval (CI) 1.08-2.99]; $P = 0.020$) and black race (HR 1.69 [95% CI 0.86-3.08]; $P = 0.104$) were associated with increased mortality compared with white race in unadjusted analysis (N = 609; Table 3). A multivariable Cox regression model adjusting for demographic variables including age at diagnosis, race/ethnicity, and smoking (n = 568) showed that Asian (HR 2.42 [95% CI 1.38-4.14]; $P = 0.001$) and black patients (HR 2.1 [95% CI 1.05-3.89]; $P = 0.026$) still had an increased risk of mortality compared with white patients.

After adjusting for the aforementioned variables and SSc-related covariates (including cutaneous subtype [diffuse vs. limited], BMI, pulmonary hypertension on echocardiogram, interstitial lung disease, scleroderma renal crisis, and malabsorption syndrome) (n = 505), Asian patients still had an increased risk of mortality (HR 1.80 [95% CI 0.99-3.16]; $P = 0.047$) (Table 3) on multivariable Cox regression. Other variables associated with higher mortality included older age at SSc diagnosis, male sex, diffuse cutaneous disease, suspected pulmonary hypertension on echocardiogram, interstitial lung disease, and malabsorption syndrome.

Leading overall causes of death (as determined by the treating physician) included highly suspected or confirmed pulmonary hypertension, multiorgan failure, infection, and cancer (Table 4). Of the 16 patients who had a primary cause of pulmonary hypertension listed as the cause of death, half had an RHC that confirmed a diagnosis of pulmonary arterial hypertension and the other half had strong clinical suspicion for pulmonary hypertension, such as a reduced global right ventricular systolic function or right ventricular hypertrophy on echocardiogram and/or clinical signs of right heart failure requiring medical management. Asian patients were most likely to die from pulmonary hypertension and infections; black patients, multiorgan failure; Hispanic patients, pulmonary hypertension; and white patients, pulmonary fibrosis. However, the numbers of deaths in each category were small.

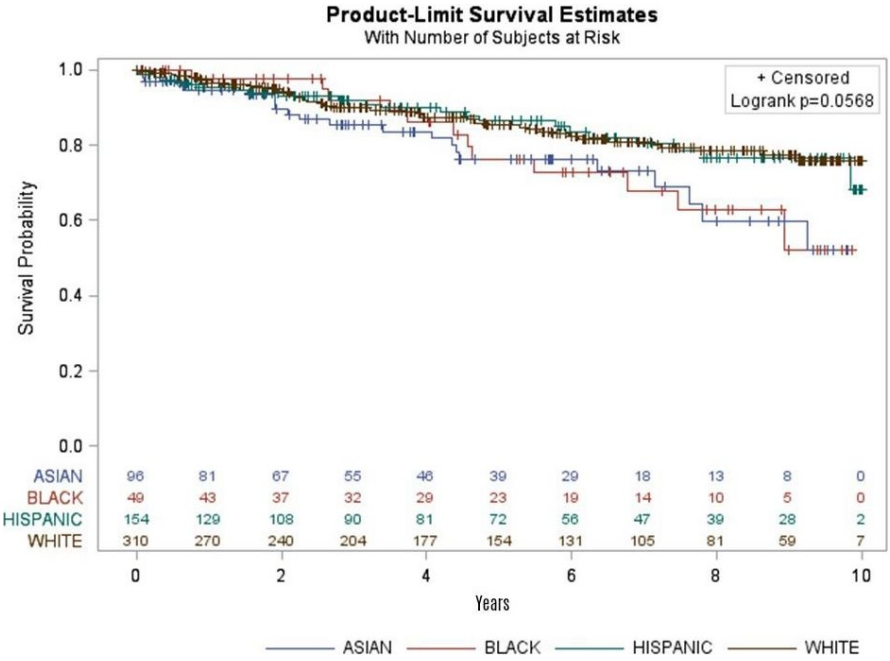


**Figure 1.** Kaplan-Meier Survival Curve by Race/Ethnicity from Diagnosis of Systemic Sclerosis.

**Medication use.** There were no statistically significant differences in exposure to medication by race/ethnicity for mycophenolate mofetil, methotrexate, cyclophosphamide, prednisone, or rituximab (Table 5). Compared with white patients, black patients had increased azathioprine exposure (16% vs. 9%) and Asian patients had increased IVIG use (7% vs. 2%), but the results were not statistically significant after adjusting for pairwise comparisons, and the frequencies were small.

**Missing data.** There were no statistically significant differences in missingness of variables assessing baseline demographics, disease duration, internal organ involvement, or medication use by race/ethnicity. Overall, there were more missing data on autoantibodies, but the data still exceeded 70% completeness in each racial/ethnic group, and autoantibodies were not included in the Cox regression models.

## DISCUSSION

Racial/ethnic differences in clinical features, autoantibody profiles, and survival among KPNC patients with SSc were demonstrated in this study. Importantly, we found that Asian patients had a more severe clinical phenotype than non-Hispanic white patients. Similar to prior studies, Asian patients in our cohort had a younger age at disease diagnosis (14,22) and higher prevalence of diffuse cutaneous disease (13,15,22), interstitial lung disease

**Table 3.** Univariable and multivariable Cox regression analysis of variables associated with overall mortality[a]

| Variables | Univariable Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Age at diagnosis, y (continuous) | **1.05** | 1.03-1.07 | <0.001 | **1.05** | 1.03-1.07 | <0.001 |
| Sex, female vs. male | **0.45** | 0.28-0.76 | 0.002 | **0.55** | 0.31-1.02 | 0.045 |
| BMI < 25 kg/m$^2$ | 1.17 | 0.73-1.90 | 0.426 | 1.05 | 0.65-1.71 | 0.843 |
| BMI ≥ 30 kg/m$^2$ | **1.03** | 0.56-1.82 | 0.007 | 0.80 | 0.43-1.46 | 0.474 |
| SSc subtype, diffuse vs. limited | **2.30** | 1.51-3.43 | <0.001 | **1.81** | 1.05-3.06 | 0.029 |
| Ever smoker | 1.46 | 0.97-2.16 | 0.063 | 1.09 | 0.69-1.68 | 0.131 |
| Asian[b] | **1.83** | 1.08-2.99 | 0.020 | **1.80** | 0.99-3.16 | 0.047 |
| Black[b] | 1.69 | 0.86-3.08 | 0.104 | 1.21 | 0.55-2.46 | 0.619 |
| Hispanic[b] | 1.03 | 0.62-1.68 | 0.895 | 1.06 | 0.60-1.81 | 0.846 |
| Pulmonary hypertension | **3.74** | 2.51-5.63 | <0.001 | **2.33** | 1.48-3.68 | <0.001 |
| Interstitial lung disease | **2.29** | 1.56-3.39 | <0.001 | **1.68** | 1.07-2.65 | 0.025 |
| Scleroderma renal crisis | **3.58** | 1.45-7.21 | 0.001 | 1.58 | 0.69-3.53 | 0.309 |
| Malabsorption syndrome | **2.59** | 1.53-4.17 | <0.001 | **2.11** | 1.17-3.60 | 0.009 |

Abbreviation: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SSc, systemic sclerosis.
[a]Statistically significant values are in bold.
[b]White patients as the reference group.

**Table 4.** Causes of death by race/ethnicity for systemic sclerosis cohort

| | Overall (N = 105) | Asian (n = 22) | Black (n = 12) | Hispanic (n = 23) | White (n = 48) |
|---|---|---|---|---|---|
| Causes of death, n (%) | | | | | |
| Atherosclerotic cardiovascular or cerebrovascular disease | 7 (6.7) | 1 (4.5) | ... | 1 (4.3) | 5 (10.4) |
| Cancer | 12 (11.4) | 2 (9.1) | 3 (25.0) | 2 (8.7) | 5 (10.4) |
| Gastrointestinal | 4 (3.8) | ... | 1 (8.3) | 2 (8.7) | 1 (2.1) |
| Infection | 13 (12.4) | 5 (22.7) | ... | 2 (8.7) | 6 (12.5) |
| Multiorgan failure | 16 (15.2) | 4 (18.2) | 4 (33.3) | 3 (13.0) | 5 (10.4) |
| Pulmonary fibrosis | 11 (10.5) | 1 (4.5) | 1 (8.3) | 2 (8.7) | 7 (14.6) |
| Pulmonary hypertension | 16 (15.2) | 5 (22.7) | 1 (8.3) | 4 (17.4) | 6 (12.5) |
| Renal crisis | 1 (1.0) | ... | ... | 1 (4.3) | ... |
| Sudden death | 3 (2.9) | 1 (4.5) | ... | 1 (4.3) | 1 (2.1) |
| Other | 11 (10.5) | 2 (9.1) | ... | 3 (13.0) | 6 (12.5) |
| Unknown | 11 (10.5) | 1 (4.5) | 2 (16.7) | 2 (8.7) | 6 (12.5) |
| Cumulative death (N = 609), n (%) | 105/609 (17.2) | 22/96 (22.9) | 12/49 (24.5) | 23/154 (14.9) | 48/310 (15.5) |

(3,13,22,23), and anti-Scl-70 antibodies (13,15,22) compared with white patients. Consistent with prior studies, Asian patients were more likely to test positive for anti-U1-RNP and anti-SSA/Ro antibodies (14,24). In this cohort, we found that Asian patients had an increased mortality compared with white and Hispanic patients, with survival rates similar to those of black patients. Asian race was associated with a higher mortality even after adjusting for multiple confounders, suggesting that these patients warrant close monitoring for progressive disease and potentially more aggressive management. Pulmonary hypertension was one of the leading causes of death in Asian patients, indicating a severe vascular phenotype in this group as well. Immunosuppressant medication use was generally similar among all groups, except for slightly higher rates of azathioprine and rituximab exposure in black patients and of IVIG exposure in Asian patients. Given the variations in practice among different providers, we are unable to comment on reasons for treatment differences. However, these differences were not statistically significant on pairwise comparisons, and the numbers were small.

The variability of disease expression among racial groups in our study suggests that multiple factors linked to race, including genetic and environmental factors, may influence clinical manifestations, disease course, autoantibody status, and mortality in SSc. There is likely a complex interplay between multiple genetic and environmental factors contributing to the increased disease severity and mortality that we observed in Asian patients in our cohort. The causes for population variation in health outcomes in our study are likely multifactorial and may include biological, environmental, and social determinants.

Genetic heterogeneity among races may significantly impact the complex phenotype of SSc and provides a biologic basis for variations in disease severity. Multiple studies have shown that genetic differences between racial groups play an important role in modulating clinical manifestations, disease progression, and autoantibody profiles in SSc. In the multicenter Genome Research in African American Scleroderma Patients (GRASP) cohort, the largest genetic study in black patients with SSc to date, there was no association between increased SSc susceptibility and genes previously implicated in European Americans (including the *ATP8B4* gene) (25). Multiple HLA antigen alleles have also been strongly associated with SSc and its clinical or serological subsets, and these associations have been found to vary in different racial/ethnic populations. For example, Han Chinese patients with SSc were more likely to have HLA-DPB1*03:01 and to develop pulmonary fibrosis (26); Thai SSc patients had increased allele frequencies of HLA-DR*15 associated with positive anti-Scl-70 antibodies (27); and DRB1*15 was associated with anti-Scl-70–positive Chinese patients with SSc, consistent with South African and Korean

**Table 5.** Exposure to immunosuppressant medications in systemic sclerosis cohort by race/ethnicity (N = 609)

| | Overall (N = 609), % | Asian (n = 96), % | Black (n = 49), % | Hispanic (n = 154), % | White (n = 310), % | *P* |
|---|---|---|---|---|---|---|
| Azathioprine | 11 | 12 | 16 | 14 | 9 | **0.035** |
| Cyclophosphamide | 7 | 8 | 10 | 7 | 6 | 0.651 |
| IVIG | 3 | 7 | 2 | 3 | 2 | 0.056 |
| Methotrexate | 27 | 28 | 30 | 27 | 25 | 0.870 |
| Mycophenolate mofetil | 24 | 26 | 32 | 29 | 20 | 0.077 |
| Prednisone (maximum) | | | | | | |
| Low dose (≤20 mg) | 43 | 35 | 52 | 46 | 42 | 0.187 |
| High dose (>20 mg) | 26 | 29 | 24 | 22 | 27 | 0.594 |
| Rituximab | 4 | 6 | 9 | 5 | 3 | 0.170 |

Abbreviation: IVIG, intravenous immunoglobulin.
Statistically significant values (defined as $P < 0.05$) are in bold.

patients with SSc (28). Genetic studies have also identified small nucleotide polymorphism haplotypes in the fibrillarin-1 gene that strongly associate with SSc susceptibility in Choctaw (a homogeneous group with a high prevalence and severe phenotype of SSc) and Japanese patients (2). These studies highlight the identification of genetic factors that may contribute to the biologic pathways affecting SSc susceptibility and expression. Further genomic research through large multicenter, multiracial cohorts is needed to investigate why certain populations have a higher susceptibility for disease and predisposition for more severe clinical manifestations. A better understanding of the biologic basis for genetic differences observed in SSc will hopefully lead to the development of targeted therapies for particular subpopulations.

The impact of environmental factors and social determinants on mortality in SSc warrants further investigation because prior studies have shown conflicting results. Some studies have demonstrated that socioeconomic status, including education level and income, has no impact on incidence or mortality in SSc (29,30), and the relative risk of death remained higher in black patients compared with white patients in a US study even after adjusting for multiple covariates, including insurance status (5). In contrast, Moore et al (31) recently reported that black patients with SSc had more severe pulmonary disease and higher unadjusted mortality compared with matched non–African American patients, but race was not a significant risk factor for mortality after adjusting for socioeconomic factors. In a recent study evaluating a large and diverse cohort of Canadian patients with SSc, there was no difference in short-term survival across ethnicities (European-descended white [n = 745], Afro-Caribbean [n = 58], South Asian [n = 70], East Asian [n = 80], Hispanic [n = 30], Arab [n = 9], First Nations [n = 7], and Persian [n = 6]), but East Asian patients interestingly had the longest median survival (32). Unlike most studies (including ours), their cohort occurred in the setting of a publicly funded universal health care system, where all citizens and permanent residents are eligible for public health insurance.

The same Canadian group also found no ethnic differences in survival in systemic lupus erythematosus (SLE) at their center, in contrast to differences reported at other centers without universal health care (33). The authors suggested that previously observed racial/ethnic disparities in survival may be partially attributed to access-to-care issues or health inequities. It is certainly possible that universal health care may improve access to care and decrease health inequities/disparities, resulting in overall more homogeneous outcomes. Our cohort at KPNC was unique because all members were insured, including those covered by Medicaid and Medicare, and had established care with a general rheumatologist, thereby allowing relatively equal access to medical services. Furthermore, as an integrated health care system, Kaiser Permanente has been cited as a leader in the field of health equity initiatives, with several formalized quality improvement programs aimed at reducing health disparities in the general population (34). However, we acknowledge that even within the KPNC insured population, it is still possible that differential access to care across races/ethnicities could still occur and potentially influence SSc disease course and mortality.

The impact of immigration patterns, generational status (foreign-born vs. native-born), and acculturation of immigrants on the clinical expression of SSc is also not known. Long-term survival could potentially be influenced by cultural variations in health-seeking behaviors, adherence, and cultural medical practices. In the general population, data from the US Department of Health and Human Services suggest that health, life expectancy, mortality, and morbidity patterns for immigrants and native-born individuals vary considerably in the United States, with health patterns varying across racial/ethnic groups (35). A comparative study of Hispanic patients with SLE residing in the United States and Mexico found that Mexican patients were more educated, had better health-related quality of life, and had overall less systemic SLE manifestations (36). The discrepant findings observed between these two groups of Hispanic patients with SLE in different geographic locations may reflect socioeconomic or biological factors, but this has not been studied extensively in SSc. Given the global phenomenon of immigration, further research in SSc is needed to understand the overall course and outcome of various racial/ethnic groups to prevent undesirable outcomes.

Our study has many strengths. First, our study population at KPNC is racially/ethnically diverse and closely approximates the general population of Northern California (17). This setting offers a unique opportunity to study the impact of race on SSc, allowing direct racial/ethnic comparisons from the same cohort instead of using historical controls. Second, we reviewed all individual electronic medical records to confirm incident SSc diagnoses and to obtain patient-level data, including organ involvement and medication usage. Finally, because KPNC is an integrated health care system, we had longitudinal follow-up survival data from both inpatient and outpatient settings.

Our study has some limitations. Our study population was cared for by multiple rheumatologists in a community-based health care organization; thus, our results may not generalize to other health care settings. In particular, this study did not include the uninsured population, patients who receive health care in a fee-for-service or nonintegrated setting, or those referred to academic medical centers in the United States specializing in the care of patients SSc. It is possible that patients with milder disease expression were more likely to be seen within KPNC compared to medically complex cases referred to academic medical centers. However, even in a relatively homogeneous population of insured patients, we found significant racial/ethnic differences in disease severity and mortality; these disparities could potentially be amplified in other health care settings but requires further investigation. Given the large number of variables per patient in this study, we only collected organ complications as binary categorical variables (ever or never); thus, we were unable to run the Cox regression analysis using time-varying covariates. As with the nature of retrospective studies, missing data were unavoidable, including data

on RNA polymerase III and assessment of the severity of skin disease. Insufficient power precluded comparisons among individual Asian subgroups based on analysis of country and ethnic origin. Finally, it was not within the scope of this study to ascertain types of insurance coverage for each member of the study cohort, which also may have changed over time regarding deductibles and copayments. Our study did not collect information on socioeconomic status, including education level, income, or primary language spoken in the household.

In conclusion, clinical characteristics and outcomes in patients with SSc varied by racial/ethnic background within the KPNC population, with poor survival in Asian and black patients. Asian race was independently associated with a higher mortality, with pulmonary hypertension being a leading cause of death in this group. Close surveillance for disease progression and screening for pulmonary hypertension should be considered in this high-risk population. Further research is needed to validate our findings in other cohorts and to identify both genetic and environmental determinants of SSc disease expression in different racial/ethnic groups. Understanding racial/ethnic variations in disease outcomes is critical because this will improve our ability to provide personalized medicine by informing patient counseling, appropriate baseline screening, and monitoring of disease progression.

## ACKNOWLEDGMENTS

We thank Kristin Sainani, PhD, for reviewing a draft of the manuscript and Chi-Mei Liu, PhD, for her research assistance with the KPNC Institutional Review Board.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published and take responsibility for the integrity of the data and the accuracy of the data analysis.

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